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EXAMINER	
LONG, SCOTT	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,180	SHORTMAN ET AL.	
	Examiner	Art Unit	
	SCOTT LONG	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *13-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☒ Claim(s) *4-6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/24/08 and 8/25/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Examiner acknowledges the election, with traverse, of Group I directed to a method for preventing onset of an autoimmune disease comprising administering Flt-3, in the reply filed on 7 January 2009.

The applicant traverses the examiner's restriction requirement. The examiner had used Maliszewski et al. (Pathol. Biol. 2001; 49: 481-483) as a basis for his opinion that the present claims do not present any special technical feature and therefore there is a lack of unity. The applicant argues, to establish unity of invention, "[a]pplicant's should be given the opportunity to argue on the merits during prosecution whether the claims are novel and unobvious over the cited prior art [Maliszewski et al., Pathol. Biol. 2001; 49:481-483]." (Remarks, page 2, parag.4). The applicant also states, "[r]estriction of the claims at this stage would deny Applicants such an opportunity."

The examiner in making the lack of unity restriction in compliance with the Unity of Invention Rules 13.1 and 13.2. According to those rules, a group of inventions is considered linked to form a single general inventive concept where there is a technical relationship among the inventions that involves at least one common or corresponding special technical feature. The expression special technical features is defined as meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art. The examiner stated that he considered the technical feature of claim 1 to be "modulating dendritic cells by administration of Flt-3" as a species of the claimed method. The examiner cited

Maliszewski et al. and described the teachings with correspond to the technical feature. In so doing, the examiner has satisfied his obligation under Rules 13.1 and 13.2.

The applicant has not submitted a rationale why Maliszewski et al. does not teach the technical feature of the instant claims, as asserted by the examiner. The logic provided by the applicant is contrary to the Unity of Invention Rules 13.1 and 13.2 applied to 35 USC 371 National stage applications, such as the instant application. There is no basis for the examiner to rejoin the Groups prior to prosecution, without an explanation why the holding of Lack of Unity was improper.

Because no argument for the traversal was provided by applicant, thus the traversal is non-persuasive and the restriction is made final.

Claim Status

Claims 1-27 are pending. However, claims 13-27 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-12 are under current examination.

Oath/Declaration

The oath or declaration, having the signatures of all inventors, received on 11 October 2006 is in compliance with 37 CFR 1.63.

Information Disclosure Statement

The Information Disclosure Statements (IDS) filed on 24 June 2008 and 25 August 2006 consisting of 2 sheets are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements.

Priority

This application claims benefit as a 371 of PCT/AU04/01840 (filed 12/23/2004) which claims priority from Foreign Application, AUSTRALIA 2003907195 (filed 12/24/2003). The instant application has been granted the benefit date, 24 December 2003, from the Foreign Application, AUSTRALIA 2003907195

Claim Objections

Claims 4-6 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim *cannot depend from any other multiple dependent claim*. See MPEP § 608.01(n). Accordingly, claims 4-6 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in *Wands* states: "Enablement is not precluded by the necessity for some 'experimentation.'" Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the

breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

NATURE OF THE INVENTION

The breadth of the claims encompasses methods of preventing onset of a large genus of autoimmune diseases.

The specification (and claim 11) indicate that particular autoimmune diseases encompassed by the method of prevention can be: Active Chronic Hepatitis, Addison's Disease, Anti-phospholipid Syndrome, Atopic Allergy, Autoimmune Atrophic Gastritis, Achlorhydra Autoimmune, Celiac Disease, Crohns Disease, Cushings Syndrome, Dermatomyositis, Type I Diabetes, Discoid Lupus, Erythematosis, Goodpasture's Syndrome, Grave's Disease, Hashimoto's Thyroiditis, Idiopathic Adrenal Atrophy, Idiopathic Thrombocytopenia, Insulin-dependent Diabetes, Lambert-Eaton Syndrome, Lupoid Hepatitis, Lymphopenia, Mixed Connective Tissue Disease, Multiple Sclerosis, Pemphigoid, Pemphigus Vulgaris, Pernicious Anema, Phacogenic Uveitis, Polyarteritis Nodosa, Polyglandular Auto. Syndromes, Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis, Psoriasis, Raynauds, Reiter's Syndrome, Relapsing Polychondritis, Rheumatoid Arthritis, Schmidt's Syndrome, Scleroderma - CREST, Sjogren's Syndrome, Sympathetic Ophthalmia, Systemic Lupus Erythematosis, Takayasu's Arteritis, Temporal Arteritis, Thyrotoxicosis, Type B Insulin Resistance, Ulcerative Colitis and Wegener's Granulomatosis. More particularly, claim 12 indicates that autoimmune (Type-1) diabetes can be prevented by the claimed method.

GUIDANCE & WORKING EXAMPLES

The specification does not provide guidance for or working examples for preventing onset of autoimmune diseases. The focus of the working examples are directed to murine diabetic mouse models. The working examples utilize Non-Obese Diabetic (NOD) which is known as an animal model for type 1 diabetes. Non-obese diabetic (NOD) mice exhibit a susceptibility to spontaneous development of autoimmune insulin dependent diabetes mellitus (IDDM). No working examples are provided which encompass the larger genus of autoimmune diseases described in claim 11, beyond the limited experiments on NOD mice.

In the NOD mice experiments, the applicants determined whether an animal had become diabetic by measuring urine and blood sugar levels (Example 3). Throughout their experiments (Figs. 4 & 5; Examples 12 & 14), the inventors indicated that some NOD mice which were treated with Flt-3L were not diabetic after certain days of treatment. The examiner points out that the claims are directed to prevention of autoimmune disease and not to lack of blood sugar. The specification indicates that at the end of the experiments, histological sections of pancreas were taken from both diabetic and non-diabetic mice. The specification indicates "[s]ome insulitis (mononuclear cell invasion of the pancreas) was seen in the protected, Flt-3L treated mice, but destruction of β-cells was markedly reduced" (page 47, lines 28-29). The specification asserts that onset of diabetes was achieved after several 10-day treatments of Flt-3L; however, since there are histological evidence of autoimmune

effect, the examiner concludes that a skilled artisan would interpret this evidence as indicating the autoimmune disease was not prevented. In addition, the specification states, "there was no reduction in diabetes incidence; the onset of diabetes was simply delayed" (page 48, lines 18-19). So, the examples of the instant specification cannot support claims for "preventing onset of an autoimmune disease."

In addition, the specification fails to show an example of an Flt-3-Flt-3L receptor agonist used to prevent onset of an autoimmune disease. The specification indicates that rational drug design may be used to generate small molecules or polypeptides which act as Flt-3-Flt-3L receptor agonists. An agonist is a ligand or drug that binds and alters the activity of a receptor. An agonist by itself would not necessarily have the activity of preventing onset of an autoimmune disease. Perhaps a combination of Flt-3L and an agonist to the receptor with binds Flt-3L would affect autoimmune disease, but that is not what is claimed. The specification indicates that Flt-3-Flt-3L receptor agonist is not a combination, but merely an agonist. Since the specification does not provide an example of an agonist by itself having the activity of preventing onset of an autoimmune disease, the specification has not enabled such an embodiment.

In addition, for the sake of compact prosecution, the examiner is addressing methods comprising co-administration of Flt-3 ligand and a Toll-like receptor (as in claims 4-6). Example 6 of the instant specification shows an *in vitro* method in which dendritic cells are cultured with the Toll-like receptor 9 agonist, oligo-CpG. However, this is not an example of a method comprising co-administration of Flt-3L and Toll-like receptor (as in claims 4-6). In addition, Rifkin et al. (Immunological Reviews 2005; 204:

27-42) suggest that Toll-like receptor ligands may play a role in the pathogenesis of autoimmune diseases such as systemic lupus erythematosus. Because the prior art indicated that administration of Toll-like receptor ligands induces autoimmune diseases encompassed by the instant claims, notably systemic lupus erythematosus (recited in claim 11), the examiner concludes that there is some unpredictability in making and using the claimed invention.

The absence of working examples directed to preventing onset of autoimmune diseases necessitates further experimentation. Therefore, the specification does not provide sufficient guidance on how to make and use the instantly claimed invention.

STATE OF THE ART & QUANTITY OF EXPERIMENTATION

The state of the art teaches that prevention of autoimmune diseases (and in particular autoimmune diabetes) is not a highly successful technique or has highly variable results.

Diabetes mellitus type 1 (type I diabetes, T1D, T1DM, IDDM, juvenile diabetes) is a form of diabetes mellitus. Type 1 diabetes is an autoimmune disease that results in destruction of insulin-producing beta cells of the pancreas. Numerous sources indicate that there is currently no clinically useful preventive measure against developing type 1 diabetes. In particular, WebMD states, "Currently there is no way to prevent type 1 diabetes" (http://diabetes.webmd.com/tc/type-1-diabetes-prevention ; last updated November 21, 2006). Most of the currently available art indicates that some of the complications related to type 1 diabetes, such as eye, kidney, heart, blood vessel and

nerves diseases can be delayed or prevented through various treatments. However, this is not the same a preventing onset of the disease itself.

In addition, regarding claims 9-10, directed to wherein the Flt-3L is derived from the same or different species to which it is administered, the specification indicates that there is some variation in results which makes practicing the claimed method somewhat unpredictable.

Consequently, there is ample reason to conclude that there would be a high degree of unpredictability in practicing the instant invention and undue amount of experimentation would be required to make and use the instant invention.

CONCLUSION

In conclusion, given the breadth of the claims, the limited scope of the specification, and state of the art, an undue quantity of experimentation is require to make and use the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Maliszewski (Pathol. Biol. 2001; 49: 481-483).

Claim 1 is directed to a method for preventing onset of an autoimmune disease in a subject said method comprising administering to said subject Flt-3l [Flt-3 Ligand] or a Flt-3-Flt-3L receptor agonist in an amount effective to increase a sub-type of non-activated, immature and tolerogenic DC selected from Plasmacytoid DC and CD8+ DC or their equivalents thereby inducing or maintaining immune tolerance in said subject. While the examiner has written a lack of enablement for "preventing onset of an autoimmune disease," the examiner applies the art of Maliszewski to the extent that he teaches the method steps of the recited claims.

Maliszewski teaches "an approach is to directly expand and/or activate DC *in vivo* using the cytokine Flt3 Ligand" (abstract). Maliszewski teaches "Flt3 Ligand (FL)…can drive large expansion of at least two mouse DC subsets….One DC subset, lymphoid-related DC (LDC), appear to selectively enhance Th1-like immune responses" (page 482, col.1, parag.1). Maliszewski also teaches Flt-3 Ligand may have its greatest effects when combined with cytokines…[thereby] increasing the ability of FL-expanded DCs to stimulate CD8+ T cells" (page 482, col.1 bridging col.2). Additionally,

Maliszewski indicates this type of therapy is useful for treatment of autoimmunity (page 482, col.2, last parag.).

Claim 2 is directed to the method of claim 1, wherein the agent is Flt-3L. Maliszewski teaches administration of Flt-3 Ligand.

Claim 3 is directed to the method of claims 1 or 2 wherein the Flt-3L or a Flt-3-Flt-3L receptor agonist is co-administered with a cytokine. Maliszewski also teaches Flt-3 Ligand may have its greatest effects when combined with cytokines" (page 482, col.1).

Claim 7 is directed to the method of claim 1 wherein the subject is a human, non-human primate, livestock animal, laboratory test animal, a companion animal, a captured wild animal or an avian species. Maliszewski is a review article which cites models applied to a laboratory mouse and humans.

Claim 8 is directed to the method of claim 7 , wherein the subject is a human. Maliszewski is a review article which cites applying their method to humans.

Claim 9 is directed to the method of claim 1, wherein the Flt-3L is derived from the same species to which it is administered. In particular, Maliszewski is a review article which cites models where the Flt-3L is derived from the same species to which it is administered.

Accordingly, Maliszewski anticipates each of the specific limitations of the instant claims. It is acknowledged that Maliszewski does not specifically teach that this would result in preventing the onset of an autoimmune disease in a subject as set forth in the preamble of the instant claim, but because the teachings of Maliszewski provide the

same method step, any outcome of practicing this step would naturally flow from the method.

Conclusion

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**. The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Scott Long/
Patent Examiner, Art Unit 1633